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Mechanisms Of Antidiarrhoeal Effect Of Piper nigrum

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Abstract: *Piper nigrum*, family - Pipereraceae (Black pepper) is a common food ingredient. Effect of fruits of *Piper nigrum* on adrenergic receptors, potassium channels and nitric oxide pathway was studied for its antidiarrhoeal activity in mice. Glibenclamide (potassium channel blocker), Isosorbide dinitrite (nitric oxide donor) has reduced the antidiarrhoeal activity of *Piper nigrum*. Antidiarrhoeal activity of *Piper nigrum* was not influenced by Yohimbine (α_2 adrenergic receptor blocker). The results obtained establish the involvement of potassium channels and nitric oxide pathway but not the α_2 adrenergic receptors in antidiarrhoeal activity of *Piper nigrum*

Key Words: *Piper nigrum*, potassium channels, nitric oxide pathway, adrenergic receptors.

INTRODUCTION

Piper nigrum, family - Pipereraceae (Black pepper) is considered as the 'King of Spices' due to the highest volume of international trade the among all the spices.[1] *Piper nigrum* is an aromatic pungent warming herb that lowers fever and improves digestion. Either powdered or its decoction is widely used in traditional Indian medicine. The ancient Aryans considered it as a powerful remedy for various disorders of the anatomical system and prescribed it as an effective cure for dyspepsia, malaria, delirium, tremors and hemorrhoids.[2,3] It is used in ayurvedic medicine to stimulate the digestive system and used for the treatment of nausea, lack of appetite and other dyspeptic complaints. In Chinese medicine it is used to treat food poisoning, stomach chills, cholera, dysentery and vomiting caused by hypothermia. In west it is used for digestion and relieving gas.[1,4] Present study was done to investigate different cellular pathways responsible for antidiarrhoeal activity of *Piper nigrum*.

MATERIALS AND METHODS

Drugs

i) Glibenclamide – Sigma Chemicals Ltd. ii) Isosorbide dinitrate – Sigma Chemicals Ltd. iii) Yohimbine – Sigma Chemicals Ltd.

4.2 Plant material and preparation of the extract

Fruits of *Piper nigrum*, (family Piperaceae) were purchased from local market. The botanical identification of the fruits was done by Dr. Dhabe, Herbarium incharge Department of Botany, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad (M.S.), India, where a voucher specimen has been deposited. After collection, the fruits were ground to coarse powder. 200 gm of the powdered fruit was boiled with 2 lit of distilled water in a conical flask for 30 min and the liquid was decanted. The resultant filtrate was evaporated to dryness in the oven at 40 °C. The dried aqueous *Piper nigrum* extract was reconstituted in distilled water.

Animals

Swiss albino mice of either sex, weighing 20 – 25 gm obtained from VIPER, Pune, were used for the experiments. They were kept in standard environmental condition, fed standard food and water ad libitum. All experiments were performed after an overnight fast. The Institutional Animal Ethical Committee of Government College of Pharmacy, Aurangabad, Maharashtra, India (GCPA/IAEC/2011/235, 11/03/2011), approved the study.

Acute toxicity study

Piper nigrum was studied for acute oral toxicity as per revised OECD guidelines number 423. Aqueous *Piper nigrum* extract were devoid of any toxicity up to 2000 mg/kg in albino mice by oral route hence dose of 300 mg/kg of aqueous *Piper nigrum* extracts was used.

Antidiarrhoeal activity of *Piper nigrum* with Isosorbide dinitrate, Glibenclamide and Yohimbine on castor oil induced diarrhoea.

Groups of six mice each were treated as outlined below:

Group 1 (Control group): Distilled water 10 ml/kg, p.o.,

Group 2 (Test group): *Piper nigrum* 300 mg/kg, p.o.,

Group 3 (Test group): Isosorbide dinitrate 150 mg/kg, p.o. (given 30 min prior to the administration of *Piper nigrum* 300 mg/kg, p.o.),

Group 4 (Test group): Glibenclmide 1 mg/kg, p.o. (given 30 min prior to the administration of *Piper nigrum* 300 mg/kg, p.o.)

Group 5 (Test group): Yohimbine 1 mg/kg, s.c. given 30 min prior to the administration of *Piper nigrum* 300 mg/kg, p.o.).

Castor oil (0.2 ml/mouse) was given to each mouse after 30 minutes. Mice were placed under separate glass funnels, with the floor lined with blotting paper and were observed for 4 hrs. The parameters studied were: onset of diarrhoea, total weight of stool output, total weight of wet stool, total number of stool output, and number of wet stool.[5,6,7]

Statistics

The results of all experiments were reported as mean ± S.E.M. Statistical analysis was carried out using Student's '*t*'-test. A level of significance of $P < 0.05$ was regarded as statistically significant.

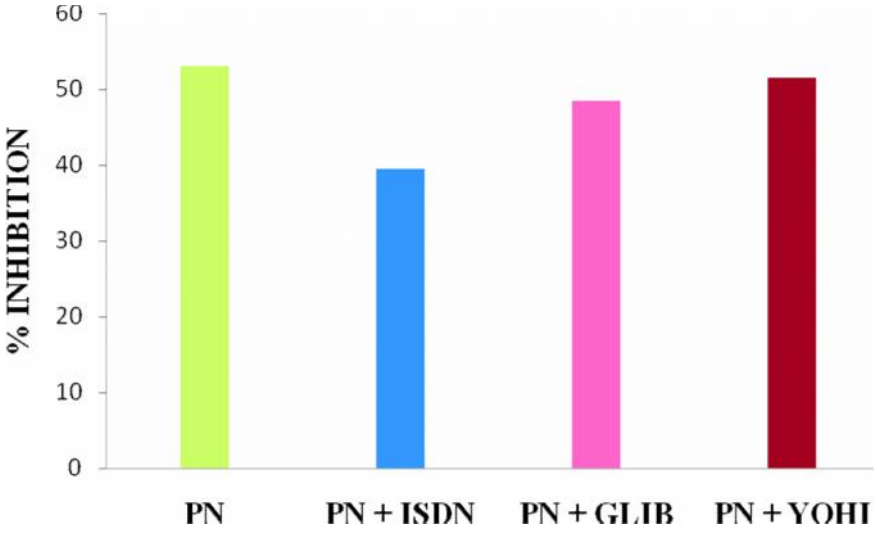
RESULTS

5.1.5 Influence of Yohimbine, Glibenclamide and Isosorbide dinitrate on antidiarrhoeal effect of *Piper nigrum* in mice.

In the course of observation for 4 h after castor oil administration, all the mice in control group produced copious diarrhoea. Pretreatment of mice with the *Piper nigrum* caused a significant dose dependent delay in the onset of copious diarrhoea, decrease in the frequency of purging (reduction of number of wet stools and total no of stools), weight of wet stools, and total weight of stools.

Piper nigrum (2.5 ml/kg) showed 53.09% inhibition of diarrhoea. With isosorbide dinitrate (150 mg/kg), glibenclamide (1 mg/kg) and yohimbine (1 mg/kg) *Piper nigrum* showed 39.45%, 48.54% and 51.54% inhibition of diarrhoea respectively.

Figure 1: Antidiarrhoeal effect of *Piper nigrum* with Isosorbide dinitrate, Glibenclamide and Yohimbine in mice.



The 'X' axis represents the dose of the drug, The 'Y' axis represents percent inhibition of diarrhoea. PN – *Piper nigrum* (300 mg/kg), ISDN - Isosorbide dinitrate (150 mg/kg), G - Glibenclamide (1 mg/kg), Y - Yohimbine (1 mg/kg).

DISCUSSION

Nitric oxide (NO) serves to protect the integrity of the mucosal barrier in the gastrointestinal (GI) tract. It stimulates gastric mucus secretion by GI epithelial cells, which helps further protect the mucosal barrier from injury.[8] In the GI tract it mediates functions like maintenance of mucosal integrity, mucosal blood flow, and maintenance of vascular tone. Castor oil induced diarrhoea and intestinal secretion involves NO as one of the mediator.[9] It is revealed that Isosorbide dinitrate (NO donor) has reduced the antidiarrhoeal effect of *Piper nigrum*.

K^+ channels are present in both mucosal and serosal membranes of colon. K^+ channels play a role in cellular volume regulation.[10] Cell volume dependent activation of K^+ channels is needed to counterbalance the cellular increase in osmolytes.[11] K^+ channels may play an important role in mediating enhanced colonic K^+ secretion in secretory diarrheal diseases.[12] Antidiarrhoeal effect *Piper nigrum* was decreased by Glibenclamide, a Potassium channel blocker drug.

The sympathetic nervous system controls the balance between absorption and secretion in the ileum through activation of mucosal α_2 adrenoceptors.[13] Stimulation of these receptors in the ileum results in a decrease in ion fluxes, consistent with the ability of α_2 adrenoceptor agonists to inhibit intestinal fluid secretion.[14,15] Antidiarrhoeal activity of *Piper nigrum* was not changed by Yohimbine (α_2 adrenergic receptor antagonist)

CONCLUSION

Nitric oxide pathway and potassium channels play an important role in the antidiarrhoeal effect of *Piper nigrum* while α_2 adrenergic receptors are not involved in the antidiarrhoeal effect of *Piper nigrum*.

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